Sub F' Cont'd

20. (New) The composition of claim 1, further comprising an agent selected from the group consisting of an anti-oxidant, surfactant, buffer, pH adjusting agent, bacteriostatic agent, stabilizer, sodium chloride, and preservative.

Q 2 Cont

21. (New) The composition of claim 1, wherein the composition is administered to the subject one to five times a day.

22. (New) The composition of claim 1, wherein the subject is a human.

REMARKS

In the Office Action dated June 15, 2001, claims 1-10 were rejected. In response to the Office Action claims 1-4 are amended, and claim 11-22 are added. Upon entry of this Amendment, claims 1-22 are pending and under consideration in the present application. Applicant respectfully submit that no new matter has been added by way of this Amendment.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-4 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that the term "relative volumetric ratios amounts" in claim 1 is a relative term which renders the claim indefinite." The claim has been amended to better define the invention. Reconsideration and withdrawal of this rejection is requested.

The Examiner further stated that claims 2-4 are vague and indefinite, as it is not clear what the mL is referring to. The claims have been amended to better define the invention. Reconsideration and withdrawal of this rejection is requested.

Rejection Under 35 U.S.C. § 103

Claims 1-10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Touitou (U.S. Patent No. 5,716,638) in view of Peart *et al.* (WO 00/24362) and Vachon (XP-000965573) in further view of Allison's Apothecary.

The Applicants respectfully disagree and traverse this rejection. Touitou in view of Peart *et al.* and Vachon in further view of Allison's Apothecary do not teach or suggest the claimed invention, nor is there any suggestion to one of ordinary skill in the art that there is a reasonable likelihood of success of the present claimed invention. Additionally, unexpected results are indicia of unobviousness.

The burden of establishing a *prima facie* case of obviousness lies with the Examiner. In determining obviousness, one must focus on the invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 USPQ 2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is: "Whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success.... Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988). When all the prior art is considered together, a person having ordinary skill in the art must have a sufficient basis for the necessary predictability of success to sustain a rejection under 35 U..S.C § 103. See Ex parte Novitski 26 USPQ2d 1389 (Bd.Pat.App. & Int. 1993) Citing In re Clinton, 188 USPQ 365 (CCPA 1976).

As it now stands before the Patent Office, claim 1 claims a stable composition for rapid delivery by inhalation to the lungs and subsequently to the bloodstream. The composition comprises a therapeutically effective amount of delta-9-tetrahydrocannabinol in

a pharmaceutically-acceptable semiaqueous solvent comprising an alcohol, water and a glycol, in amounts sufficient

(i) to aerosolize the composition to a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and

(ii) to enhance partitioning by producing a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol.

Claims 2-10 recite the composition of claim 1.

Touitou teaches liposomal compositions for topical application to the skin where the compositions contain phospholipid, ethanol, water and propylene. A skin permeation enhancing system containing THC is provided in Table 1. In this permeation enhancing system, THC and the phospholipid Phospholipon 90 (PL-90) are dissolved in an ethanol-propylene glycol (EtOH-PG) mixture with gentle heating while mixing. Water is then added with vigorous stirring. See Table 1, column 5, and column 6, lines 41-42. In another example the permeation enhancing system described above is made into a ethosomal preparation by slowly adding PVP/VA while stirring and then sonicating the solution in 3 cycles of 5 minutes with 5 minutes rest between each cycle. Column 6, lines 44-46. In another example, an ethosomal preparation contains 0.1% THC, 5% PL-90, 35% isopropyl alcohol, 5% PG, and 54% water. See Table 7, column 16. However, Touitou does not teach or suggest the present claimed invention of a composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising an alcohol, water and a glycol, for rapid delivery by inhalation to the lungs, and subsequently to the bloodstream. Additionally, Touitou does not teach the amounts of THC, alcohol, water and glycol that are sufficient (i) to aerosolize the composition to a mean mass median aerodynamic diameter in the range from about 1 up to

about 10 μM; and (ii) to enhance partitioning by producing a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol.

Peart *et al.* teach an aerosol-dispensable non-aqueous composition comprising a non-CFC propellant and delta-9-tetrahydrocannabinol. An organic solvent such as ethanol can be used to assist in solubilizing the THC in the propellant but is not required. However, Peart *et al.* do not teach or suggest the present claimed invention of a stable composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising an alcohol, water and a glycol, for rapid delivery by inhalation to the lungs, and subsequently to the bloodstream. Additionally, Peart *et al.* teach non-aqueous compositions and do not teach the amounts of THC, alcohol, **water** and glycol that are sufficient (i) to aerosolize the composition to a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and (ii) to enhance partitioning by producing a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol. Semiaqueous solutions, that is combinations of organic solvents with small, effective amounts of water, lend themselves to making formulations with delta-9-tetrahydrocannabinol with unexpected increases in partitioning, apparently because the drug has a poor affinity for the water within the formulation. Because of the increased ease of partitioning, once released deeply in the lung from the dosage forms of the present claimed invention, delta-9-tetrahydrocannabinol is able to cross cell membranes rapidly, traverse the alveolar epithelial cells, interstitium, and endothelium to reach the blood stream. See page 5, lines 4-19.

Vachon *et al.* teach that the airways respond to aerosolized THC. The vehicle of the composition is disclosed as propylene glycol and water in a ratio of 9:1. The concentration of THC is disclosed as 4.5 g/100 ml. However, Vachon *et al.* do not teach or suggest the

present claimed invention of a stable composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising an alcohol, water and a glycol, for rapid delivery by inhalation to the lungs, and subsequently to the bloodstream. Additionally, Vachon *et al.* do not teach the amounts of THC, **alcohol**, water and glycol that are sufficient (i) to aerosolize the composition to a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and (ii) to enhance partitioning by producing a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol.

Allison's Apothecary teaches amber glass bottles that come with an atomizer. This reference also does not teach or suggest the present claimed invention.

Furthermore, there is no motivation to combine the cited references. The Office Action stated that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the invention with Touitou with the teaching of Peart *et al.* and obtain an aerosolized composition because a) Touitou and Peart *et al.* both teach a composition comprising tetrahydrocannabinol for therapeutic use; and b) Touitou and Peart *et al.* teach compositions of similar sizes. The Office Action further stated that it would have been obvious to one or ordinary skill in the art at the time of the invention was made to have modified the invention of the combined references by using the teachings of Vachon *et al.* and obtain a higher ratio of propylene glycol in the solvent system because a) Touitou and Peart *et al.* all teach compositions comprising tetrahydrocannabinol as the active agent; b) Touitou and Peart *et al.* teach propylene glycol as solvents; c) Vachon *et al.* teach that increasing the propylene glycol:water ratio increases the clarity of the composition. Additionally, the Office Action further stated that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of

the combined references with that of Allison's Apothecary and obtain a multi-dosage form container comprising Type I Amber Glass because a) Vachon *et al* teach administration via a multi dosage nebulizer; b) Peart *et al,* teach that the containers for the formulations of the instant invention may be any that are suitable for the efficacious delivery of aerosol inhalants and that have various dose metering chambers.

However, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (MPEP 2143.01 citing In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

In making this unsupported statement of interchangeability, the Office Action is attempting to shift the burden of proof of unobviousness to the Applicants. In the 35 U.S.C. §103(a) rejection of present claims, the Office Action has cited no pertinent reference teaching or suggesting the claimed invention or suggesting to one of ordinary skill in the art the interchangeability of elements in the present claims.

Furthermore, there is no expectation of success when combining the teaching of Touitou with that of Peart *et al.* and Vachon in further view of Allison's Apothecary. The compositions taught in Touitou contain lipophillic excipients, such as PL-90, for topical applications and does not teach if these excipients can even be aerosolized. These lipophillic excipients are also not desirous for rapid absorption of a lipophillic drug, such as THC, into the blood system, as the drug will not partition readily because the drug has a strong affinity for the excipient resulting in slow absorption of the drug.

Additionally, Touitou provides no suggestion or teaching of how these topical liposomal compositions would be administered by inhalation or aerosolized at a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM. For delivery to

the lung a formulation must be aerosolized to a particle size less than or equal to about 10 μM to reach the lung, and the drug must readily partition out of the delivery system in order to transport across biological membranes and reach the blood system. Again, Touitou teaches topical applications, not aerosolized formulations.

Additionally, Peart *et al.* teach non-aqueous compositions and do not teach the amounts of THC, alcohol, **water** and glycol that are sufficient (i) to aerosolize the composition to a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and (ii) to enhance partitioning by producing a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol.

Vachon *et al.* also do not teach the amounts of THC, **alcohol**, water and glycol that are sufficient (i) to aerosolize the composition to a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and (ii) to enhance partitioning by producing a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol.

The Office Action therefore has cited no pertinent reference teaching or suggesting the present claimed invention or suggesting to one of ordinary skill in the art the interchangeability of elements in the present claims.

Additionally, unexpected results are indicia of unobviousness. As can be seen from Table 1 on page 8 of the present application, in varying ratios of ethanol/propylene glycol, THC is able to remain in solution in the presence of controlled amounts of water. However, as the water content increases and ethanol content decreases beyond a certain level, THC readily falls out of solution. As mentioned above, semiaqueous solutions of the present claimed invention lend themselves to making formulations with delta-9-tetrahydrocannabinol with unexpected increases in partitioning, because the drug has a poor affinity for the water within the formulation. Because of the increased ease of partitioning, once released deeply in

the lung from the dosage forms of the present claimed invention, THC is able to cross cell membranes rapidly, traverse the alveolar epithelial cells, interstitium, and endothelium to reach the bloodstream. The data presented in Table 3 on page 10 of the present application shows that a semiaqueous formulation of THC in accordance with the present invention can produce a stable clear solution near the solubility point of THC. Moreover, because THC has poor affinity for the formulation, it is able to partition out and transport across cell membranes to reach the bloodstream quickly. This is demonstrated by the comparative t_{max} values achieved *in vivo* in single dose intravenous and 14 day multiple dose inhalation studies conducted in dogs and rats. See Table 3. These data show that when delta-9-tetrahydrocannabinol is maintained near the solubility point of the drug, unexpectedly, partitioning is enhanced and *in vivo* bioavailability is enhanced.

Therefore, the cited references do not teach or suggest the claimed invention, nor do they suggest to one of ordinary skill in the art that there is a reasonable likelihood of success. Also, the Office Action has cited no pertinent reference suggesting to one of ordinary skill in the art the interchangeability of elements of the present claims. And furthermore, unexpected results are indicia of unobviousness. The 35 U.S.C. § 103(a) rejection is therefore improper. Reconsideration and withdrawal of this 35 U.S.C. §103(a) rejection is requested.

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 1-22 are in condition for allowance. It is respectfully submitted in view of the foregoing Remarks that all of the objections and rejections in the Office Action dated June 15, 2001 have been overcome and should be withdrawn. Accordingly, reconsideration and withdrawal of the outstanding rejections and allowance of claims 1-22 is respectfully solicited. Applicant respectfully requests early and favorable notification to that effect.

Respectfully submitted,

Dated: October 15, 2001 By: _____

Joseph A. Mahoney
Registration No. 38,956
Mayer, Brown & Platt
P.O. Box 2828
190 S. LaSalle Street
Chicago, IL 60690-2828
(312) 701-8979

Version with Markings to Show Changes Made to the Claims

1. (Amended) A stable composition for rapid delivery by inhalation by a subject to the lungs, and subsequently to the bloodstream, the [said] composition comprising a therapeutically effective amount of delta-9-tetrahydrocannabinol in a pharmaceutically-acceptable semiaqueous solvent comprising an alcohol, water and a glycol, in [relative volumetric ratio] amounts sufficient

(i) to aerosolize the composition to a mean mass median aerodynamic diameter in the range from about 1 up to about 10 μM; and

(ii) to enhance partitioning by producing a stable clear solution near the solubility point of the delta-9-tetrahydrocannabinol.

2. (Amended) A composition as defined in Claim 1 wherein the [said] amount of delta-9-tetrahydrocannabinol comprises from about 0.1 to about 200 mg delta-9-tetrahydrocannabinol/mL of the solvent.

3. (Amended) A composition as defined in Claim 2 wherein the [said] amount of delta-9- tetrahydrocannabinol comprises from 0.1 to 25 mg delta-9-tetrahydrocannabinol/mL of the solvent.

4. (Amended) A composition as defined in Claim 2 [3] wherein the [said] amount of delta-9- tetrahydrocannabinol comprises 50 mg delta-9-tetrahydrocannabinol/mL of the solvent.